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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

SM

Office Action Summary	Application No.	Applicant(s)	
	09/698,893	KRAUS ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,19-25,27,29-33,35,37 and 41-44* is/are pending in the application.

4a) Of the above claim(s) *12, 22-24, 42 and 43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-16,19-21,25,27,29-33,35,37,41 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 October 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/01/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed June 1, 2004 has been entered. Claims 1-3, 13-16, 27, 35, 37, and 44 have been amended. Claims 17, 34, 36, 40, and 45-47 have been cancelled.

Accordingly, Claims 1-16, 19-25, 27, 29-33, 35, 37, and 41-44 remain pending in the instant application.

Claims 12, 22-24, 42, and 43 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction requirement in Paper No. 8 (filed 9/16/02).

Accordingly, Claims 1-11, 13-16, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 are examined herein.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 1, 2004 has been entered.

Drawings

The drawings are objected to because the labeling of the figures is improper. The figures must be numbered consecutively. Figures 2, 2A, 3, 3A, 5, 5A, 5B, 5C, 5D must be relabelled. The next consecutive number after Figure 2, is Figure 3, not Figure 2A. Alternatively, Figure 1 may be followed by Figures 2A and 2B. Corrected drawing sheets are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet

should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Corrected drawings are required in reply to this Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Objections

Claims 37 and 41 are objected to because the claims encompass non-elected subject matter, which should be deleted from the claims. The claims are directed to treating any disorder of the central nervous system, but the elected invention is limited to methods of treating stroke. The claims encompass treating conditions other than stroke, as well as treating healthy patients. Appropriate correction is required.

Claims 13 and 16 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 13 requires that the improvement result in repair of central nervous system damage caused by said stroke. Claim 16 requires that the improvement

comprises measurable stroke recovery. This is not further limiting because Claims 1, 2, and 3 all require an improvement in function of the central nervous system. In order for a functional improvement to be observed, it would necessarily have to be measurable.

Double Patenting

Applicant is advised that should Claim 1 be found allowable, Claim 4 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). When Claim 4 depends from Claim 2, the Claim 4 is identical to Claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1-11, 13-16, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are referred to the final guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, Number 4, pp. 1099-1111 (also available at www.uspto.gov).

Applicants are reminded that the written description requirement is severable from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), *cert.* denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (While acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, the Federal Circuit reaffirmed that under 35 U.S.C. 112, first paragraph, the written description requirement is separate and distinct from the enablement requirement and gave an example thereof). An invention may be described without the disclosure being enabling (e.g., a chemical compound for which there is no disclosed or apparent method of making), and a disclosure could be enabling without describing the invention (e.g., a specification describing a method of making and using a paint composition made of functionally defined ingredients within broad ranges would be enabling for formulations falling within the description but would not describe any specific formulation). See *In re Armbruster*, 512 F.2d 676, 677, 185 USPQ 152, 153 (CCPA 1975).

The Guidelines for Written Description specifically state that "[t]he claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art" (Federal Register, Vol. 66, No. 4, page 1105, column 1).

The cell composition used for transplantation is an essential element of the claimed invention. The specification states that the cells administered may be "CD34+/-, Lin- cells separated from cord blood" (page 6, lines 16-17). The specification further asserts in the Example section that "CD34+/-, Lin- cells" were administered to the rats. The specification relies on U.S. Patent No. 5,925,567 for teaching how to obtain "CD34+/-, Lin- cells" (page 6, lines 21-23). In the Example section, the specification states that the "CD34+/-, Lin- cells" used in the example "were selected from a sample of fresh cord blood cells using the procedure described in Example 5 of U.S. Patent No. 5,925,567" (page 10, lines 9-11). The specification does not

further describe "CD34+/-, Lin- cells," nor does it define the meaning of the designation "CD34+/-". While one of skill in the art would understand that "Lin-" cells do not express the Lin marker, one of skill in the art would not understand the meaning of "CD34+/-". The term is not defined in the specification and is not conventional in the art. Example 5 of U.S. Patent No. 5,925,567 does not describe the preparation of "CD34+/-, Lin- cells." Example 5 describes the preparation of CD34- cells from the mononuclear fraction of umbilical cord blood. The patent does not describe "CD34+/-, Lin- cells."

Given that the specification discloses that the cell composition used in the Example comprises "CD34+/-, Lin- cells," one of skill in the art would not know the identity of the cell composition that produced the result described therein. Further, given the limited details for obtaining the cell composition used in the Example of the specification, the skilled artisan would not know how to obtain the requisite cell composition for transplantation. This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the cell compositions required for use in the claimed method, at the time the application was filed. Furthermore, the instant specification does not place the public in possession of the cell compositions. Thus, it is concluded that the written description requirement is not satisfied for the claimed methods of cell transplantation.

Enablement

Claims 1-11, 13-16, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of causing an improvement in function of the central nervous system of a subject having impaired central nervous system function by administering "an aliquot of CD34+/-, Lin- cells." The cells may be derived from umbilical cord blood or other blood sources.

The specification discloses an example at pages 10-13 where male Sprague Dawley rats were subjected to an MCA occlusion and subsequently received an injection of "CD34+/-, Lin- stem cells" directly into the ischemic region of the brain. Some modest improvement was observed in two of the behavioral tests that the animals were subjected to following treatment; specifically, the forelimb placing test and the hindlimb placing test. No improvement was observed in 3 other behavioral tests that the animals were subjected to (i.e., swinging, cylinder, or paw reaching tests).

While the Example is limited to transplantation of a specific cell type (CD34+/-, Lin-) isolated from a sample of fresh cord blood, for the reasons discussed herein above, the skilled artisan would not know what is meant by "CD34+/-" and would not be able to obtain the cells referred to in the Example section. Furthermore, the Example does not specify from which animal species the cells were isolated, although it does state that cyclosporin was administered to the rats. Furthermore, the "aliquot of CD34+/-, Lin- cells" is not disclosed as being a homogeneous cell population, and is therefore understood to comprise a variety of other cell types.

The state of the art is such that very little is known about the cell types that can be used to restore neurological function. One of the lingering questions in the field of stem cell research relates to the stage of differentiation of stem cells useful for transplantation and whether the same stage will be useful for all transplantation applications, or vary on a case-by-case basis (see p. ES-8, column 1 of Stem Cells: Scientific Progress and Future Research Directions, June 2001).

In a review of the state of the art of stem cell technology, the National Institutes of Health acknowledge the potential usefulness of stem cells in theraeutic transplantation and the possible development of therapeutic protocols in the future (see Stem Cells: Scientific Progress and Future Research Directions, June 2001). However, the review also illustrates that there are numerous and significant obstacles that must be overcome. As such, the asserted utility of the present invention, directed to using the claimed methods in therapeutic transplantation to treat stroke constitutes a credible utility, albeit one that is not enabled by the instant specification. The instant rejection therefore is not for lack of utility, but rather for lack of enablement for the asserted utility. For the reasons discussed herein, the specification does not teach how to use the claimed methods to produce a therapeutic effect nor does it adequately teach how to practice the claimed method, which covers transplantation of a variety of cell types, as well as combined administration of cells and growth factors.

The specification fails to provide an enabling disclosure for the method of cell-based therapy because methods of transplantation of stem cells, precursor cells, and neural tissue into the CNS are not routinely successful and the specification does not offer adequate guidance to overcome the unpredictability in the art to enable one skilled in the art to practice the claimed method over the full scope to derive a therapeutic benefit in a diseased animal. The specification teaches that the only use for the claimed method of transplantation is to produce a therapeutic effect, but the specification does not adequately teach how to carry out the claimed methods to produce such an effect. Jackowski et al. (1995) details the limitations and unpredictability associated with transplantation of neural tissue. At page 311, column 1, paragraph 2, the reference discusses barriers to successful transplantation of neural tissue, notably the presence of molecules that actively inhibit the regeneration of mammalian CNS axons.

The specification fails to provide an enabling disclosure for producing a therapeutic effect using the claimed methods of therapeutic transplantation because the specification does not

provide **specific guidance** for transplanting appropriate cell compositions or for the combined administration of various cells and growth factors. In unpredictable arts, it is the specification itself that must provide the novel teachings for carrying out the claimed methods therapeutically. The working example is limited to transplantation of a specific cell type (CD34+/-, Lin-) isolated from a sample of fresh cord blood, into a rat that serves as a stroke model, but the specification does not adequately describe the cell type or its method of preparation. The specification contemplates that "cells of the invention" can be used to treat a wide variety of neurodegenerative diseases, including stroke, Huntington's disease, Parkinson's disease, Alzheimer's disease, ALS, multiple sclerosis , Tay-Sacks, and cerebral palsy (page 4, lines 8-9). However, the elected invention is limited to methods of treating stroke. Accordingly, the specification must teach how to practice the full scope of the claimed methods of transplantation to produce a therapeutic effect in a patient having suffered from a stroke. The specification fails to provide specific guidance relating to the cell compositions required to provide a therapeutic benefit for stroke.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

Given the limited working examples, the limited guidance provided in the specification, the broad scope of the claims with regard to the various cell compositions to be transplanted and the combinations of cells and growth factors to be administered, and the unpredictability for producing a therapeutic effect upon transplantation of stem cells or precursor cells, undue experimentation would have been required for one skilled in the art to practice the claimed methods of transplantation to produce a therapeutic effect in a stroke patient.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 13-16, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11, 13-16, 19-21, 25, 27, 29-33, 35, and 44 are indefinite in their recitation of "CD34+/-, Lin- cells" because the term "CD34+/-" is not defined in the specification and is not conventional in the art. Thus, it is unclear what the "CD34+/-" designation means. It is therefore unclear what cell type is to be used in the claimed method.

Claim 14 is indefinite in its recitation of "central nervous system disease caused by said stroke" because stroke does not **cause** CNS disease. Stroke is typically a **result of** cerebrovascular disease.

Claims 25 and 31 are indefinite in their recitation of "intercerebrally" because one of skill in the art would understand the term to refer to brain tissue or fluid-filled space that lies **between** the two cerebral hemispheres, but the specification does not define the term "intercerebrally" as it is being used in the context of the claims. Thus, it is unclear what brain structures would be considered to lie between the two cerebral hemispheres. Nothing in the specification suggests

injecting the cell composition into the cerebrospinal fluid that lies between the two cerebral hemispheres. The metes and bounds of the claims are not clearly set forth.

Claims 25 and 31 are indefinite in their recitation of "intercerebrally, intracisternally, intracebroventricularly" because Claims 1 and 2, from which Claims 25 and 31 depend, are already limited to administering the cells "directly to the site of said stroke." The "site of said stroke" would necessarily be located within the brain tissue and therefore would not be located in the fluid-filled spaces such as the ventricles.

Claims 37 and 41 are indefinite in their recitation of "plurability" because "plurability" is not a word.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-11, 13-16, 19-21, 25, 27, 29-33, 35, 37, 41, and 44 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent Application Publication No. 2002/0028510 A1 (Sanberg et al.; published March 7, 2002; filed March 9, 2000), as evidenced by Rosu-Myles et al. (2000, Stem Cells 18: 374-381).

The claims are directed to a method of causing an improvement in function of the central nervous system of a subject having impaired central nervous system function resulting from a stroke.

Sanberg et al. (2000) disclose a method for treating stroke by administering umbilical cord blood cells. Claim 39 recites "a method of treating a patient with a neurodegenerative disease comprising administering an effective number of neural cells in umbilical cord blood or a mononuclear fraction therof to said patient." Claim 40 specifically recites treating ischemia. Claim 64 recites "a method of treating a patient in need thereof for a neurodegenerative disease other than amyotrophic lateral sclerosis, said method comprising administering an effective amount of human umbilical cord blood or a mononuclear cell fraction thereof to said patient." Claim 65 specifically recites treating ischemia. The disclosure explicitly contemplates using the method of the invention to treat stroke (paragraphs [0042], [0054], [0065], and paragraphs {0161] through [0233]). The reference discloses significant functional recovery in a rat stroke model (paragraph [0231]).

The reference of Sanberg et al. inherently discloses administration of a cell composition comprising Lin- cells, as recited in the claims, because human cord blood cells inherently comprise Lin- cells, as evidenced by Rosu-Myles et al.

Thus, the claimed invention is disclosed in the prior art.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571)272-0728. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571)272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Dianiece Jacobs, whose telephone number is (571) 272-0532.

Anne-Marie Falk, Ph.D.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER